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Comparison of Carbon-11–Acetate With Fluorine-18–Fluorodeoxyglucose for Delineating Viable Myocardium by Positron Emission Tomography

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Objectives. **This study was designed to determine in patients with advanced coronary disease whether prediction of recovery of mechanical function after coronary revascularization could be accomplished more effectively by positron emission tomography (PET) with carbon-11 (^{11}C)–acetate than by PET with fluorine-18 (^{18}F)–fluorodeoxyglucose.**

Background. **Results of previous studies have demonstrated that preservation of myocardial oxidative metabolism (measured by PET with ^{11}C-acetate) is necessary for recovery of systolic function after coronary revascularization.**

Methods. **Myocardial oxidative metabolism was quantified before revascularization in 34 patients by the analysis of the rate of myocardial clearance of ^{11}C-acetate. Metabolism of glucose was assessed by analysis of uptake of ^{18}F-fluorodeoxyglucose. Receiver operating characteristic curves for predicting functional recovery were derived for the measurements of oxidative metabolism and glucose metabolism. In addition, criteria for prediction of recovery of function based on measurements of oxidative metabolism and glucose metabolism were developed and compared.**

Results. **Analysis of receiver operating characteristic curves indicated that estimates of oxidative metabolism were more robust in predicting functional recovery than were estimates of glucose metabolism ($p < 0.02$). Moreover, threshold criteria with ^{11}C-acetate exhibited superior positive and negative predictive values (67% and 89%, respectively) than did the criteria with ^{18}F-fluorodeoxyglucose (52% and 81%, respectively), $p < 0.01$. In segments with initially severe dysfunction, estimates of oxidative metabolism tended to be more robust than estimates of glucose metabolism in predicting functional recovery. Moreover, in such segments, the threshold criteria with ^{11}C-acetate tended to exhibit superior positive and negative predictive values (85% and 87%, respectively) than did the criteria with ^{18}F-fluorodeoxyglucose (72% and 82%, respectively), although statistical significance was not achieved.**

Conclusions. **In patients with advanced coronary artery disease, the extent to which functional recovery can be anticipated after coronary revascularization can be delineated accurately by quantification of regional oxidative metabolism by PET with ^{11}C-acetate.**

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Selection of patients with impaired left ventricular systolic function who would benefit from coronary revascularization requires accurate differentiation of myocardium that is hibernating or stunned but still viable from irreversibly injured, nonviable tissue (1). We and others have explored the feasibility of utilizing cardiac positron emission tomography (PET) for this purpose. Initial clinical efforts have focused on quantifying myocardial utilization of glucose with the glucose analogue fluorine-18–fluorodeoxyglucose in patients with left ventricular dysfunction attributable to chronic coronary artery disease (2,3). Persistent myocardial utilization of glucose, reflected by accumulation of ^{18}F-fluorodeoxyglucose, has been shown to predict restoration of function after coronary revascularization. Conversely, diminished utilization concordant with the reduction in perfusion has been thought to be indicative of irreversible injury (2–6). Unfortunately, however, PET with ^{18}F-fluorodeoxyglucose overestimates the extent of tissue viability in as many as 32% of myocardial segments and underestimates tissue viability in up to 22% of segments (2,3,6). These discordances may in part reflect differences in the pattern of substrates presented to the heart at the time of myocardial imaging with ^{18}F-fluorodeoxyglucose. These re-

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sults also probably reflect the failure of uptake of ^{18}F-fluorodeoxyglucose delineated with PET to identify metabolic processes underlying viability sufficient for restoration of myocardial systolic function (7).

Under physiologic conditions, myocardial oxidative metabolism is required to support contractile function (8,9). In myocardium rendered ischemic but ultimately salvaged by reperfusion, maintenance of oxidative metabolism is required for subsequent functional recovery (10,11). We and others (12–14) have shown that PET with ^{11}C-acetate can accurately quantify regional myocardial oxidative metabolism under conditions of normoxia, ischemia or reperfusion and under diverse ventricular loading conditions. Furthermore, maintained oxidative metabolism has been found to be a more robust descriptor of functional recovery compared with maintained glucose utilization under several circumstances (15,16). Accordingly, it appeared likely that differentiation of dysfunctional but viable myocardium from nonviable tissue could be accomplished more effectively by quantification of regional myocardial oxidative metabolism by PET with ^{11}C-acetate than by measuring myocardial utilization of glucose by PET with ^{18}F-fluorodeoxyglucose.

Methods

Study patients. The protocol was approved by the Human Studies Committee and the Radioactive Drug Research Committee of Washington University School of Medicine, and written informed consent was obtained from each patient. Thirty-four patients (26 men and 8 women; mean age 60 years range 30 to 77) who had left ventricular wall motion abnormalities secondary to angiographically documented coronary artery disease were studied. Twenty-one had sustained at least one myocardial infarction from 11 days to 10 years before enrollment in the study. In 17 patients, the myocardial infarction had occurred ≥1 month before enrollment. Two patients had undergone coronary artery bypass surgery 18 and 4 years earlier, respectively. Because the kinetics of ^{18}F-fluorodeoxyglucose in myocardium have not been well delineated in patients with diabetes mellitus, patients with known diabetes were excluded.

Cardiac catheterization and selective coronary angiography followed by coronary revascularization (coronary artery bypass surgery or coronary artery angioplasty) were performed in all patients. Eight had angiographically defined lesions in a single vessel, 8 had lesions in two vessels and 18 had lesions in three vessels. In 24 patients, coronary artery bypass grafting was performed, and 10 underwent percutaneous transluminal coronary angioplasty. The adequacy of the revascularization procedure was verified by review of the operative reports documenting the successful placement of bypass grafts and, in the case of coronary angioplasty, by angiographic documentation of successful balloon dilation. None of the patients exhibited signs or symptoms of acute myocardial infarction during the interval between the performance of the initial PET and wall motion studies and performance of the follow-up wall motion study.

Assessment of ventricular function. For each patient, regional systolic function was assessed before (mean 18 days, range 1 to 65) and after (mean 2.0 months, range 0.5–7) coronary revascularization. In 20 patients, regional systolic function was assessed before and after revascularization by two-dimensional echocardiography. In six patients, contrast ventriculography was performed before and two-dimensional echocardiography after revascularization. In six patients, radionuclide ventriculography was performed before and after coronary revascularization. Two patients underwent left ventricular aneurysmectomy at the time of revascularization (see later).

Regional systolic function was quantified as recently described (15,16). For the purposes of analysis, the left ventricular myocardium was segmented into eight regions (septal, anterobasal, anterior, apical, lateral, posterolateral, inferior and inferoposterior). With all three modalities (echocardiography, radionuclide ventriculography and contrast left ventriculography), regional systolic function was graded according to the scoring system recommended by the American Society for Echocardiography (1 = normal, 2 = hypokinetic, 3 = akinetic, 4 = dyskinetic and 5 = aneurysmal) (17). The wall motion analyses were performed by two observers blinded to both PET and clinical data. The average wall motion score reflecting values assigned by both observers was tabulated for each segment in each study.

As judged from the wall motion analyses, myocardial segments were defined as: 1) normal; 2) dysfunctional but viable (initially dysfunctional segments [wall motion score ≥2] that subsequently exhibited an improved wall motion score of at least one full grade after revascularization); or 3) nonviable (persistently dysfunctional segments that did not exhibit functional improvement) (15,16). In the two patients who underwent left ventricular aneurysmectomy, only those segments that were resected were included in the analysis because of the potential for misregistration of segments identified before and after revascularization consequent to the altered left ventricular geometry that typically occurs after aneurysmectomy. Extensive transmural necrosis and scarring were confirmed by gross and microscopic analysis in each. Thus, the segments that were resected were classified as nonviable. In patients who underwent coronary artery bypass surgery, the interventricular septum was excluded from analysis because of abnormalities in contractile performance independent of ischemia that occur frequently in this region after surgery.

Tomographic assessment of perfusion and metabolism. Tomographic assessments of perfusion and metabolism were performed in all patients before coronary revascularization (mean 12 days, range 1 to 38). Positron emission tomographic studies were performed on average within 8 days (range 1 to 56) of the assessments of systolic function. Tomographic studies (16) that delineated the effects of revascularization on myocardial perfusion, oxidative metab-

olism and glucose utilization in dysfunctional but viable and nonviable myocardium have previously been reported for 16 of the patients in the current study.

The methods used to measure regional myocardial perfusion, oxidative metabolism and utilization of glucose have been reported recently in detail (15,16). In brief, PET studies were performed on standard PET instrumentation available at Washington University (18–20). All subjects were studied in the postprandial state after the consumption of a high carbohydrate meal 2 to 3 h before and 75 g of glucose (Trutol) 1 to 2 h before the administration of ^{18}F-fluorodeoxyglucose (15,16). An initial transmission scan was performed to correct subsequent emission scans for attenuation. Carbon-11–acetate (0.25 to 0.40 mCi/kg) was then administered intravenously, followed by an 1,800-s list mode data collection. Subsequently, ^{18}F-fluorodeoxyglucose (9 to 10 mCi) was administered intravenously, with an 1,800-s list mode data collection performed 45 min later. To ensure that each patient was positioned consistently within the PET system for all data collections, position was checked with the use of a low energy laser and indelible marks placed on the torso.

Regional myocardial perfusion in relative terms was based on the early myocardial uptake of ^{11}C-acetate. Results of previous studies by our group and others (21,22) have demonstrated that the regional distribution of activity within the myocardium from 60 to 180 s after the administration of ^{11}C-acetate accurately reflects regional myocardial perfusion in relative terms. Myocardial oxidative metabolism was quantified by determining the myocardial turnover rate constant of acetate (k_1), which reflects the rate of clearance of ^{11}C activity from myocardium after the administration of ^{11}C-acetate and correlates closely with regional myocardial oxygen consumption (12–14). Regional myocardial utilization of glucose was assessed on the basis of composite images of relative ^{18}F-fluorodeoxyglucose activity.

Analysis of tomographic images was performed with an operator-interactive method developed and validated in our laboratory (23). All myocardial images were reformatted from the transaxial orientation to true short-axis views, with the heart divided into 8 to 12 tomographic slices on which circumferential profiles of myocardial uptake of ^{11}C-acetate, k_1 and ^{18}F-fluorodeoxyglucose activity were generated for each. The left ventricular myocardium was segmented as for studies of wall motion, with distal slices comprising the left ventricular apex, middle slices comprising anterior, lateral, inferior and septal segments and basal slices comprising the anterobasal, posterolateral and inferoposterior segments. By reorienting the myocardial images and limiting the segmentation of left ventricular myocardium to eight large segments, the risk of misregistration of the tomographic estimates of perfusion and metabolism with the measurements of regional wall motion was reduced.

Average values for myocardial uptake of ^{11}C-acetate, k_1 and ^{18}F-fluorodeoxyglucose activity were calculated for each segment. Carbon-11 acetate myocardial uptake and ^{18}F-fluorodeoxyglucose activity were normalized to peak myocardial activity for ^{11}C-acetate and ^{18}F-fluorodeoxyglucose, respectively, to yield relative values for myocardial blood flow and utilization of glucose. In addition, myocardial utilization of glucose was normalized to blood flow within each segment by dividing normalized ^{18}F-fluorodeoxyglucose activity by normalized myocardial uptake of ^{11}C-acetate activity for the same segment, an approach analogous to that described by others (24).

Data analysis. *Generation of receiver operating characteristic curves.* Receiver operating characteristic curves for predicting functional recovery were derived from the individual estimates of regional myocardial oxidative metabolism, glucose metabolism and glucose metabolism normalized to flow in the dysfunctional segments. The shape of these curves reflects the performance of the measurements of oxidative metabolism and glucose metabolism in predicting functional recovery over a wide range of observed values.

Generation of tomographic criteria of myocardial viability. Although receiver operating characteristic curve analysis is useful for evaluating the performance of a test, for the purposes of clinical decision-making, threshold values must be used. Consequently, tomographic criteria of tissue viability and of nonviability were developed by referencing values for oxidative metabolism and utilization of glucose to mean values obtained in control subjects for each of the eight segments. The control group consisted of 10 healthy normal volunteers (9 men; mean age 24 ± 3 years) with no history of and a low likelihood for coronary artery disease. As judged from measures of myocardial oxidative metabolism, dysfunctional but viable myocardium was considered present when values for k_1 were within 2 SD of the mean value for a particular segment in the control group. Conversely, nonviable myocardium was considered present when values for k_1 were lower than the mean value minus 2 SD in the control group. These criteria were chosen on the basis of the observation that in patients with chronic coronary artery disease, the level of oxidative metabolism exhibited by dysfunctional but viable myocardium was comparable to that exhibited by normal myocardium. In contrast, the level of oxidative metabolism exhibited by nonviable myocardium was significantly lower than that in either normal or dysfunctional but viable myocardium (16). In the control subjects, mean values and standard deviations for k_1 ranged from 0.052 ± 0.007 min^{-1} in apical segments to 0.057 ± 0.006 min^{-1} in inferior segments. Criteria using measurements of myocardial utilization of glucose to identify viable myocardium were analogous to those developed and validated by others (2,3). Dysfunctional but viable myocardium was defined by values for regional myocardial utilization of glucose within 2 SD of the mean value in the control group (mean values ranged from 85 ± 11% in septal segments to 94 ± 7% in posterolateral segments). Values for myocardial utilization of glucose normalized to flow that were >2 SD above the mean value in the control group were defined as

indicative of dysfunctional but still viable myocardium. In the control subjects, mean values ranged from 0.92 ± 0.07 in inferior segments to 0.99 ± 0.14 in anterobasal segments. Conversely, reductions in myocardial utilization of glucose (values >2 SD below the mean value in the control group) that were not associated with increased utilization of glucose normalized to flow were defined as indicative of nonviable myocardium.

Statistical analysis. Continuous variables were assessed in terms of mean values and standard deviations. The comparisons of paired frequency data were performed with a continuity-corrected McNemar test. Receiver operating characteristic curves were compared with the methods of Hanley and McNeil (25,26). With this approach, it is assumed that information is conveyed by a one-dimensional variable X, with low values of X suggesting that tissue is nonviable and high values suggesting that it is viable. Then if N represents the distribution of the X values that are associated with nonviable tissue and V represents the distribution of the X values for viable tissue, the area A under the receiver operating characteristic curve is given by:

$$A = \text{Probability}(V > N).$$

With this formulation, Hanley and McNeil (25) demonstrated that the area under the receiver operating characteristic curve along with the standard error of that area can be computed with a standard Wilcoxon statistic. This is because the Wilcoxon statistic is by definition a measure of the proportion of observed X values that are associated with viable tissue that exceed a given X value that is associated with nonviable tissue, summed over all X values that are associated with nonviable tissue. Thus, the Wilcoxon statistic is completely analogous to the area under the receiver operating characteristic curve as just described. With this formula, it is a simple matter to compute the standard error (SE) of the difference between the areas under two uncorrelated receiver operating characteristic curves as:

$$SE(A_1 - A_2) = \sqrt{SE^2(A_1) + SE^2(A_2)},$$

and thereby to test the hypothesis of the equality of the areas under two uncorrelated receiver operating characteristic curves. In their second report, Hanley and McNeil (26) extended this computation of standard errors in a natural way to the case that applies herein, where the receiver operating characteristic curves being compared are derived from the same subject and are therefore correlated. Probability (p) values < 0.05 were considered significant.

Results

Systolic function. As judged from the wall motion analyses, 131 segments were identified as normal and 141 segments as dysfunctional. Twenty-five of the dysfunctional segments were excluded from further analysis because of 1) location in interventricular septum in patients undergoing coronary artery bypass surgery (n = 15); 2) location not completely within the field of view of the scanner during tomographic imaging (n = 4); 3) incomplete revascularization (n = 4); and 4) failure to completely characterize systolic function before and after coronary revascularization (n = 2). Among the 116 dysfunctional segments that were included in the analysis, 46 were classified as dysfunctional but viable and 70 as nonviable. Before revascularization, both types of dysfunctional myocardium exhibited similar mechanical impairment, with dysfunctional but viable myocardium exhibiting an average wall motion score of 2.72 ± 0.74 and nonviable myocardium showing an average wall motion score of 2.68 ± 0.91 (p = NS). After coronary revascularization, segments classified as dysfunctional but viable exhibited improvement in systolic wall function (in accordance with our original definition), with an average wall motion score of 1.28 ± 0.56. Conversely, regional wall motion in dysfunctional segments classified as nonviable did not change appreciably as evidenced by an average wall motion score after revascularization of 2.68 ± 0.89 (mean change 0.01 ± 0.30). Severe systolic dysfunction was present in 26 segments (from 13 patients) classified as dysfunctional but viable; these segments exhibited akinetic to frank aneurysmal changes (wall motion score ≥3) before coronary revascularization. Thirty-one segments (from 14 patients) classified as nonviable exhibited similarly severe impairment of function before coronary revascularization.

To determine the reproducibility of the estimates of regional systolic function, the paired wall motion studies from 10 patients (six paired echocardiograms, two paired radionuclide ventriculograms and two contrast left ventriculograms paired with echocardiograms) were chosen at random and reanalyzed. The wall motion analysis was performed by the same two observers who performed the initial analyses and who were blinded to the tomographic and clinical data as well as the wall motion scores assigned initially. In 38 dysfunctional segments, the average wall motion score calculated on repeat analysis was comparable to that calculated initially both before (2.46 ± 0.74 and 2.64 ± 0.74, respectively, p = NS, average percent difference 10.2 ± 19.0%) and after (1.88 ± 0.74 and 1.89 ± 0.81, respectively, p = NS, average percent difference between the two measurements 7.8 ± 17.5%) coronary revascularization. Moreover, the changes in systolic function in response to coronary revascularization calculated on the repeat analysis (average change 0.76 ± 0.63) were comparable to those estimated initially (0.82 ± 0.71, p = NS, average percent difference between the two measurements (18 ± 30%).

Tomographic criteria and functional outcome for all dysfunctional segments. *Analysis of receiver operating characteristic curves.* The receiver operating characteristic curves for predicting functional recovery generated for the measurements of oxidative metabolism and glucose metabolism are shown in Figures 1 and 2. Examples of dysfunctional but viable myocardium and nonviable myocardium are illustrated in Figures 3 and 4, respectively. The receiver operating characteristic curve reflecting measurements of regional

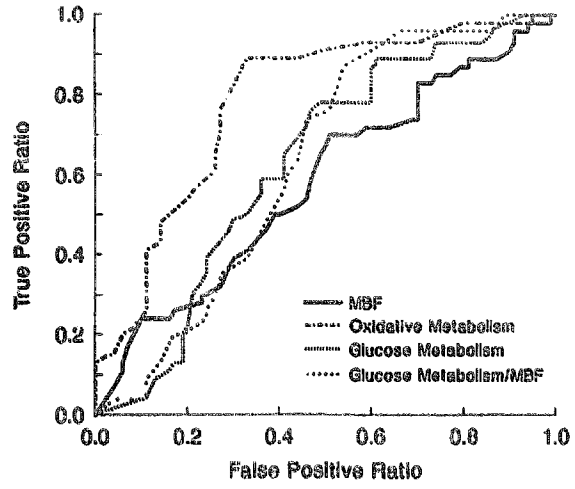
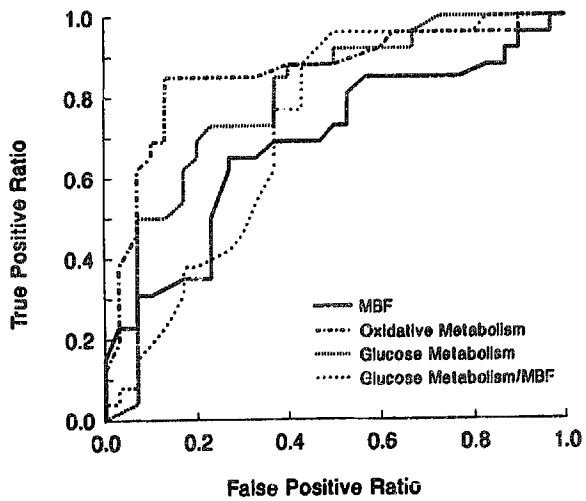


Figure 1. Receiver operating characteristic curves for prediction of functional recovery based on measurements of regional myocardial blood flow (MBF), oxidative metabolism, glucose metabolism and glucose metabolism normalized to flow. Measurements of oxidative metabolism were the most accurate as evidenced by the left and upward shift of the receiver operating characteristic curve for these measurements (area under the curve 0.79 ± 0.05) compared with the curves reflecting estimates of myocardial blood flow (area under the curve 0.58 ± 0.06, $p < 0.008$), glucose metabolism (area under the curve 0.63 ± 0.05, $p < 0.007$) and glucose metabolism normalized to flow (area under the curve 0.63 ± 0.05, $p < 0.02$).

perfusion are displayed for comparison purposes. The relatively linear shape of this curve (area under the curve 0.58 ± 0.06) suggests that measurements of relative flow alone were not useful in delineating viable myocardium. Measurements of oxidative metabolism were the most accurate in delineating viable myocardium as evidenced by the left and upward shift of the receiver operating characteristic curve for these measurements (area under the curve 0.79 ± 0.05) compared with the curves reflecting estimates of glucose metabolism (area under the curve 0.63 ± 0.05, $p < 0.007$) and glucose metabolism normalized to flow (area under the curve 0.63 ± 0.05, $p < 0.02$) (Fig. 1).

Figure 2. Receiver operating characteristic curves for predicting functional recovery in segments exhibiting severe dysfunction initially. Again, measurements of oxidative metabolism tend to be the most accurate in predicting functional recovery (area under the curve 0.78 ± 0.06) relative to the curves reflecting measurements of myocardial blood flow (MBF) (area under the curve 0.61 ± 0.08, $p <$ 0.02), glucose metabolism (area under the curve 0.72 ± 0.07, $p =$ NS) and glucose metabolism normalized to flow (area under the curve 0.64 ± 0.07, $p =$ NS).



Accuracy of threshold criteria for predicting functional outcome. As judged from the kinetics of myocardial clearance of ^{11}C-acetate activity measured before revascularization, 60 segments were identified as dysfunctional but viable and 56 segments were classified as nonviable. Before revascularization, 73 segments were classified as dysfunctional but viable as judged from the regional distribution of ^{18}F-fluorodeoxyglucose activity in myocardium; 56 segments exhibited values of regional ^{18}F-fluorodeoxyglucose activity within 2 SD of the mean value in the control group and 17 segments exhibited augmented utilization of glucose relative to flow. Conversely, 43 dysfunctional segments were classified as nonviable because they exhibited reduced myocardial accumulation of ^{18}F-fluorodeoxyglucose.

Sixty-seven percent of segments initially classified as dysfunctional but viable on the basis of PET with ^{11}C-acetate exhibited functional improvement after revascularization. In contrast, only 52% of the 73 segments initially classified as dysfunctional but viable on the basis of PET with ^{18}F-fluorodeoxyglucose exhibited improvement in systolic function ($p < 0.01$ compared with ^{11}C-acetate) (Table 1). In the 56 segments that were classified as dysfunctional but viable as judged from ^{18}F-fluorodeoxyglucose activity alone, 55% exhibited functional improvement after revascularization. In the subset of 17 segments classified as dysfunctional but viable based on the presence of augmented utilization of glucose normalized to flow, only 7 (41%) exhibited functional recovery after revascularization. Examples of discordant segment classification based on results with ^{11}C-acetate and ^{18}F-fluorodeoxyglucose are shown in Figures 5 and 6. In dysfunctional segments initially classified as nonviable by PET with ^{11}C-acetate, 89% exhibited no functional improvement after coronary revascularization. In contrast, 81% of dysfunctional segments initially classified as nonviable by PET with ^{18}F-fluorodeoxyglucose exhibited no improvement after revascularization ($p < 0.01$ compared with ^{11}C-acetate) (Table 1).

To determine if estimates of regional myocardial perfusion alone could differentiate viable from nonviable myocardium, criteria based on early myocardial uptake of ^{11}C-acetate were compared with functional outcome. Dysfunctional but viable myocardium was considered to be present when values for myocardial uptake of ^{11}C-acetate were within 2 SD of the mean value in the control group for a particular segment. Conversely, nonviable myocardium was considered to be present when values for myocardial uptake of ^{11}C-acetate were lower than the mean value minus 2 SD in the control group. In dysfunctional segments classi-

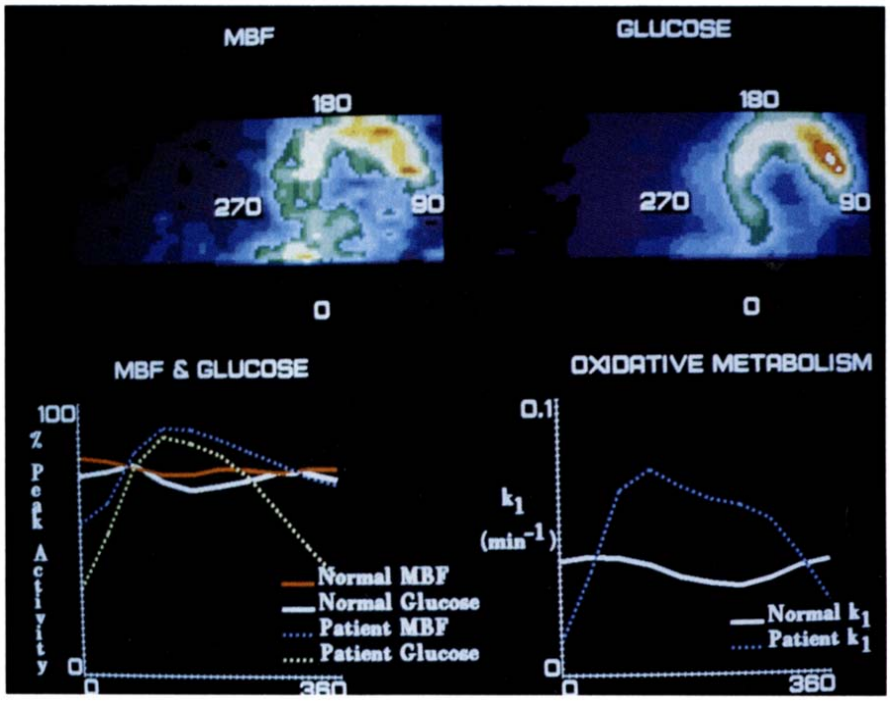


Figure 3. Flow and metabolism before revascularization in nonviable myocardium in the inferolateral wall. The midventricular images of flow (**upper left**) and glucose utilization (**upper right**) are displayed in true short-axis orientation. The lateral wall is at 90° and the anterior wall is at 180°. At the **lower left** are circumferential profiles of the relative values for regional perfusion (**blue interrupted curve**) and glucose utilization (**yellow interrupted curve**). Profiles representing the lower limits of normal (derived from the 10 normal control subjects) for regional flow and glucose utilization are depicted by the solid red and white curves, respectively. At the lower right is the profile representing regional values for the myocardial turnover rate constant of acetate (k_1) for this patient (**blue interrupted curve**) superimposed on the profile depicting the lower limits of normal (**white solid curve**). Myocardial blood flow (MBF) and utilization of glucose are reduced concordantly in the inferolateral wall, decreasing to less than the lower limits of normal, a pattern consistent with nonviable myocardium. Myocardial oxidative metabolism in the inferolateral wall also decreases to less than the lower limits of normal for this region, consistent with nonviable myocardium.

fied as viable, 45% (34 of 75) exhibited functional improvement after revascularization. Conversely, 68% (28 of 41) of dysfunctional segments classified as nonviable did not exhibit functional improvement ($p < 0.01$ compared with the myocardial clearance of ^{11}C-acetate).

Tomographic criteria and functional outcome for severely dysfunctional segments. *Analysis of receiver operating characteristic curves.* Delineation of the capacity for functional recovery is particularly difficult in regions of severe impairment. Yet, it is of particular clinical importance. Consequently, we performed a separate analysis on dysfunctional segments that exhibited frank akinetic to aneurysmal changes before coronary revascularization (Fig. 2). In the severely dysfunctional segments, measurements of oxidative metabolism tended to be better for predicting functional recovery as evidenced by the left and upward shift of the receiver operating characteristic curve (area under the curve 0.78 ± 0.06) relative to the curves reflecting measurements

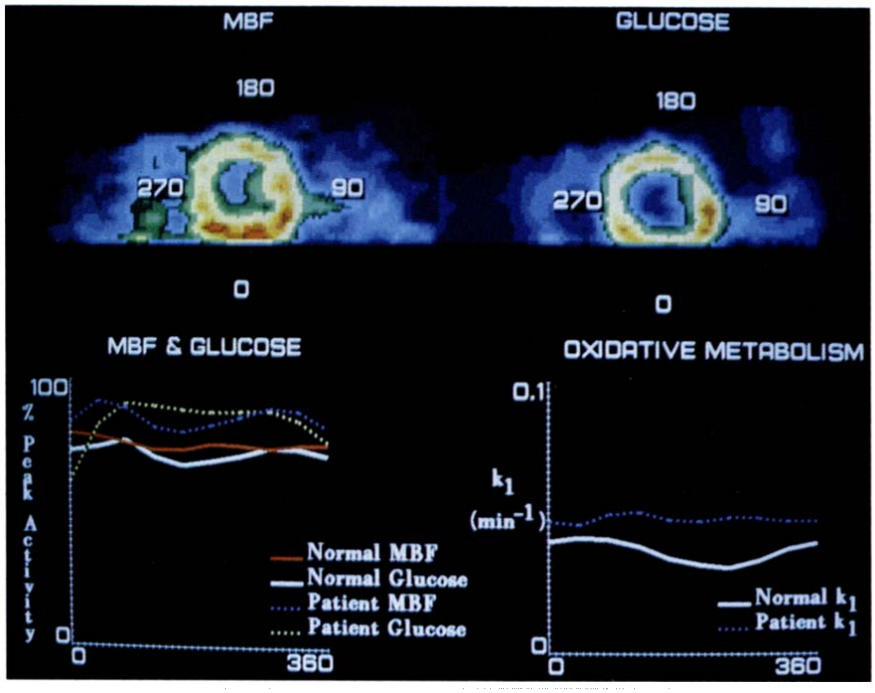


Figure 4. Flow and metabolism before revascularization in the anterior wall in dysfunctional but viable myocardium (akinesia present initially, with normal function after revascularization). In the anterior wall, both flow and glucose utilization are within the normal range predictive of functional recovery. Myocardial oxidative metabolism in the anterior wall is within the normal range as well. Abbreviations as in Figure 3.

Table 1. Tomographic Criteria of Myocardial Viability and Functional Outcome

	Wall Motion (no. of segments)		
	Improved	Not Improved	Predictive Value (%)
Fluorine-18–fluorodeoxyglucose			
Viable	38	35	52
Nonviable	8	35	81
Carbon-11–acetate			
Viable	40	20	67*
Nonviable	6	50	89*

*$p < 0.01$ compared with fluorine-18–fluorodeoxyglucose.

of glucose metabolism and glucose metabolism normalized to flow (area under the curve 0.72 ± 0.07 and 0.64 ± 0.07, respectively), but these differences did not achieve statistical significance.

Accuracy of threshold criteria for predicting recovery of function. Among segments exhibiting severe impairment in systolic function before revascularization that were classified as dysfunctional but viable by PET with ^{11}C-acetate, 85% exhibited functional improvement after revascularization. However, among segments classified as dysfunctional but viable by PET with ^{18}F-fluorodeoxyglucose before revascularization, only 72% exhibited improved systolic function after revascularization (p = NS) (Table 2). Among the 22 segments classified as dysfunctional but viable based on the level of ^{18}F-fluorodeoxyglucose activity alone, 73% (n = 16) exhibited functional improvement after revascularization. Among the seven segments classified as viable on the basis of the presence of augmented utilization of glucose normalized to flow, 71% (n = 5) exhibited functional recovery after revascularization.

In severely dysfunctional segments classified as nonviable by PET with ^{11}C-acetate, 87% did not improve after coronary revascularization. Eighty-two percent of severely dysfunctional segments classified as nonviable by PET with ^{18}F-fluorodeoxyglucose failed to exhibit improvement in systolic function after revascularization (p = NS).

In severely dysfunctional segments classified as viable on the basis of flow estimates, 56% (18 of 32) exhibited functional improvement after coronary revascularization. Sixty-eight percent (17 of 25) of severely dysfunctional segments classified as nonviable on the basis of flow estimates failed to exhibit improvement in mechanical function after revascularization ($p < 0.05$ compared with myocardial clearance of C-11 acetate).

Discussion

Our results indicate that in patients with left ventricular dysfunction attributable to predominantly chronic coronary artery disease, regional estimates of overall myocardial oxidative metabolism by PET with ^{11}C-acetate can accurately identify dysfunctional but still viable myocardium capable of recovering systolic function after coronary revascularization. They indicate that the estimates are more robust and superior to those acquired with a tracer that is not specific for oxidative metabolism.

Delineation of viable myocardium by fluorine-18–fluorodeoxyglucose. Accelerated utilization of glucose (attributable to both anaerobic and aerobic glycolysis) is characteristic of myocardium rendered ischemic (27). Consequently, initial efforts to delineate dysfunctional but viable myocardium by PET focused on assessing levels of myocardial utilization of glucose with ^{18}F-fluorodeoxyglucose in relation to functional outcome (2,3). In humans with left ventricular dysfunction attributable to chronic coronary artery disease, the persistence of myocardial utilization of glucose (whether or not hypoperfusion was present) identified myocardium capable of functional recovery after coronary artery bypass surgery in 78% to 85% of cases (2,3). Conversely, reduced myocardial utilization of glucose (concordant with reduced perfusion) identified dysfunctional myocardium that failed to improve in 78% to 92% of cases (2,3). Accordingly, PET with ^{18}F-fluorodeoxyglucose has been considered by many to be useful for differentiating dysfunctional but viable from nonviable myocardium (4–6).

Recently, positive and negative predictive values of 68% and 79%, respectively, for identifying viable myocardium with this approach have been reported (6). Thus, PET with ^{18}F-fluorodeoxyglucose will overestimate the extent of tissue viability in up to 32% of myocardial segments and underestimate the extent of tissue viability in up to 22% of segments (3,6). The discordances may be explained in part by the differences in the protocols used to standardize the substrate environment for myocardial imaging with ^{18}F-fluorodeoxyglucose in the various studies (for example, lower predictive values were reported when patients were studied under fasting conditions than when they were studied in the glucose-loaded state) (2,3,6). However, these inaccuracies probably also reflect the relative nonspecificity of myocardial kinetics of ^{18}F-fluorodeoxyglucose with respect to oxidative compared with nonoxidative myocardial glucose metabolism (7,28). Indeed, it was recently shown that myocardial accumulation of ^{14}C-deoxyglucose does not reflect glycolysis during reperfusion, whether or not hyperglycemia was present initially (7). Consequently, PET with ^{18}F-fluorodeoxyglucose may not be capable of specifically identifying those metabolic processes required for the recovery of function of myocardium rendered ischemic.

Oxidative metabolism and myocardial viability. Under physiologic conditions, maintenance of myocardial oxidative metabolism is required for continued contractile function (8,9). In experimental animals subjected to myocardial ischemia and successful reperfusion, recovery of contractile performance is associated with recovery of oxidative metabolism (10,11). Until recently, the lack of availability of methods for measurement of regional myocardial oxidative

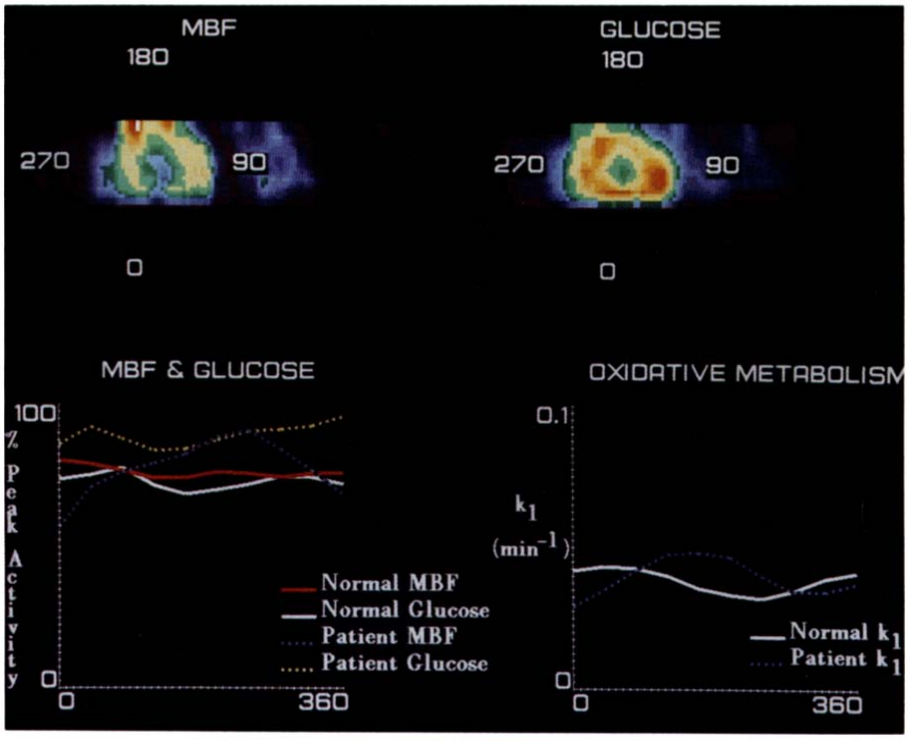


Figure 5. Nonviable myocardium (based on assessments of function before and after revascularization) in the inferior wall, where criteria for myocardial viability based on fluorine-18–fluorodeoxyglucose and carbon-11–acetate determined before revascularization were discordant. In the inferior wall, glucose utilization is increased relative to flow, a pattern considered typically to be indicative of viable myocardium. In contrast, oxidative metabolism is reduced in the inferior wall consistent with nonviable myocardium. Augmented myocardial utilization of glucose relative to flow in the presence of reduced oxidative metabolism suggests that the preserved glucose utilization is primarily anaerobic, a condition incapable of maintaining tissue viability in the long term. Abbreviations as in Figure 3.

metabolism precluded assessments in human subjects. However, results of studies by our group and others (12–14) have demonstrated that PET with acetate can provide accurate estimates of regional overall myocardial oxidative metabolism under conditions of normoxia, ischemia and reperfusion. Using this approach in conjunction with PET and ^{18}F-fluorodeoxyglucose, we demonstrated that preservation of overall myocardial oxidative metabolism is a necessary condition for the recovery of function after revascularization in patients with left ventricular dysfunction attributable to either acute or chronic coronary syndromes (15,16). Furthermore, results from these studies suggested that preservation of myocardial utilization of glucose (particularly in the presence of hypoperfusion) predicted functional recovery only when the metabolic pattern in the tissue reflected primarily oxidative utilization of glucose. Accordingly, it appeared likely that ^{11}C-acetate would more effectively predict improvement in mechanical function after coronary

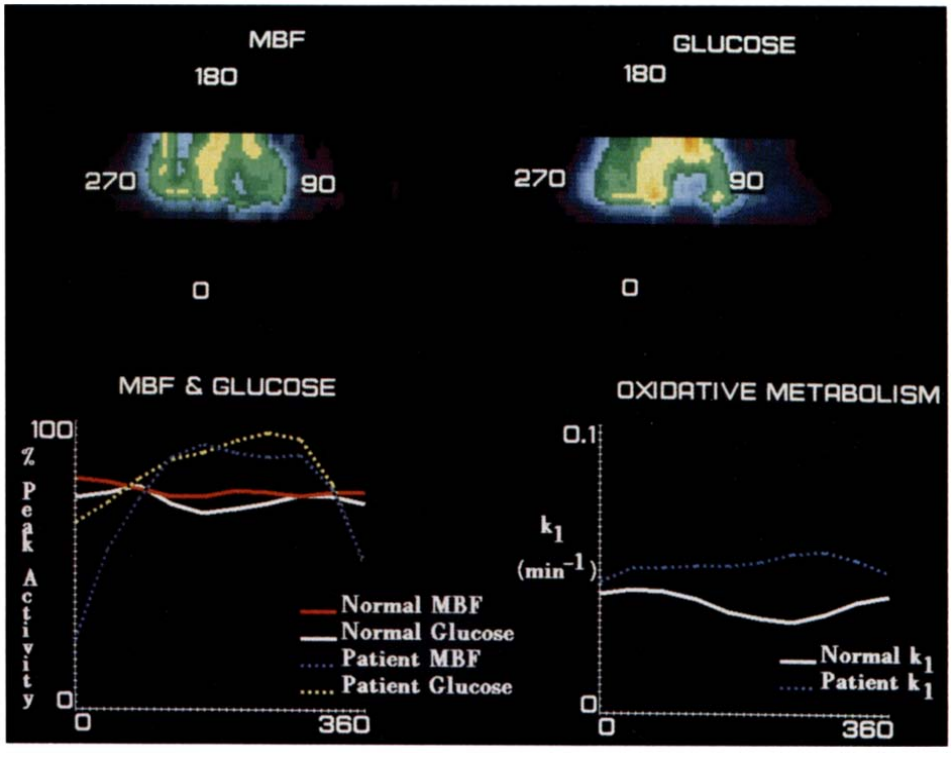


Figure 6. Viable myocardium (based on assessments of function before and after revascularization) in the inferior wall, where criteria for myocardial viability based on fluorine-18–fluorodeoxyglucose and carbon-11–acetate determined before revascularization were discordant. In the inferior wall, myocardial utilization of glucose is reduced (as is flow), suggesting the presence of nonviable myocardium. However, oxidative metabolism is maintained in the normal range consistent with viable tissue. Reduced myocardial utilization of glucose in the presence of preserved oxidative metabolism suggests other substrates (probably fatty acids) were being used to support oxidative metabolism. Abbreviations as in Figure 3.

Table 2. Tomographic Criteria of Myocardial Viability and Functional Outcome in Severely Dysfunctional Segments*

	Wall Motion (no. of segments)		
	Improved	Not Improved	Predictive Value (%)
Fluorine-18–fluorodeoxyglucose			
Viable	21	8	72
Nonviable	5	23	82
Carbon-11–acetate			
Viable	22	4	85
Nonviable	4	27	87

*Dysfunctional segments exhibiting akinetic to aneurysmal changes before coronary revascularization.

revascularization. The findings in the present study demonstrate that PET with ^{11}C-acetate is superior to PET with ^{18}F-fluorodeoxyglucose for this purpose (Tables 1 and 2; Fig. 1, 2, 5 and 6).

Because of the close coupling of myocardial oxygen consumption and perfusion, it has been theorized that estimates of myocardial oxidative metabolism by PET with ^{11}C-acetate would not be better discriminators of myocardial viability than estimates of flow. The findings in the present study suggest this is not the case in patients with left ventricular dysfunction attributable to chronic coronary artery disease. Quantification of myocardial oxidative metabolism better differentiated viable and nonviable myocardium than did estimates of relative flow, regardless of the severity of the mechanical dysfunction present initially. Quantification of regional myocardial perfusion in absolute terms might have improved the accuracy of the flow criteria for identifying viable myocardium. However, the findings in the present study are consistent with previous reports (16,29,30) suggesting that although a parallelism exists between blood flow and oxygen consumption in myocardium rendered ischemic, the actual correlation differs from that observed in normal myocardium (probably because of increased extraction of oxygen by ischemic myocardium).

Comparison with previous studies. On first inspection, the finding that only 67% and 52% of segments identified as dysfunctional but viable based on PET with ^{11}C-acetate and with ^{18}F-fluorodeoxyglucose, respectively, exhibited improvement in systolic function after coronary revascularization is somewhat surprising. Although none of the patients exhibited clinical evidence of aortocoronary bypass graft closure or restenosis of a native coronary artery, subclinical occurrences of these phenomena may have lowered the predictive values for both tracers. However, the relatively short interval from revascularization to the follow-up measurement of systolic function (average 2 months) and the lack of symptoms reduce the likelihood that graft closure or coronary restenosis contributed significantly to the results. The large number of segments (59 of 116) classified as hypokinetic before coronary revascularization is a more likely contributing factor. Such segments must have contained some myocardium that maintained residual contractile function (and thus was active metabolically). The scoring system used in the present study does not compensate for the severity of wall motion abnormalities in segments identified as hypokinetic (that is, mild, moderate or severe). Consequently, dysfunctional segments defined as initially hypokinetic (initial wall motion score 2 to 2.9) before coronary revascularization would have had to exhibit normal or near normal wall motion after revascularization to be classified as dysfunctional but viable. In contrast, a dysfunctional segment with an initial wall motion score of 3 would have had to exhibit a wall motion score after revascularization of only 2 to be classified as dysfunctional but viable. Indeed, among segments with severe dysfunction before revascularization, the positive predictive values for both PET with ^{11}C-acetate and with ^{18}F-fluorodeoxyglucose were higher (Table 2). Thus, it appears that criteria for differentiating dysfunctional but viable from nonviable myocardium on the basis of measurements of myocardial metabolism are most accurate when applied to severely dysfunctional myocardium—regions for which the distinction between viability and nonviability is of most clinical importance.

The positive and negative predictive values (based on ^{18}F-fluorodeoxyglucose criteria) of 72% and 82%, respectively, for segments exhibiting severe dysfunction initially are consistent with values reported by Tamaki et al. (3) (78% for both) and Marwick et al. (6) (positive predictive value of 68% and negative predictive value of 79%). The lower negative predictive values (Tables 1 and 2) in the current study may have been related in part to posttest referral bias. In approximately 30% of patients in the present study, tomographic information regarding myocardial viability contributed at least in part a decision on whether or not to proceed with coronary revascularization. Consequently, the number of cases in which dysfunctional segments were correctly identified as nonviable myocardium by PET with ^{18}F-fluorodeoxyglucose may have been underrepresented. However, a similar bias would have also been present for the criteria based on PET with ^{11}C-acetate. The use of different methods to measure mechanical function before and after coronary revascularization in eight of the patients could have increased the number of discordances between the tomographic criteria of tissue viability and functional outcome (see Results). However, the assessment of regional systolic function was reproducible despite the use of different imaging methods. Moreover, the accuracy of the tomographic criteria for identifying viable myocardium in severely dysfunctional segments (positive and negative predictive values of 73% and 80%, respectively) for ^{18}F-fluorodeoxyglucose and of 80% and 87%, respectively, for ^{11}C-acetate in the 26 patients in whom the paired echocardiograms or radionuclide ventriculograms were used to determine the functional response to revascularization was comparable to that of the group as a whole. Thus, it is unlikely that using different methods to assess mechanical

function before and after revascularization had a significant impact on the accuracy of the tomographic criteria for viability.

Myocardial imaging with ^{11}C-acetate: technical considerations. In addition to improved accuracy in differentiating dysfunctional but viable from nonviable myocardium, PET with ^{11}C-acetate affords logistic advantages relative to PET with ^{18}F-fluorodeoxyglucose. The duration of a complete tomographic study with ^{11}C-acetate is approximately 45 min, during which both relative myocardial blood flow and regional myocardial oxidative metabolism can be assessed. In contrast, a viability study with ^{18}F-fluorodeoxyglucose requires 2 h and the use of another radiopharmaceutical (for example, ^{15}O-water, ^{13}N-ammonia or ^{82}rubidium) for assessment of perfusion. The insensitivity of ^{11}C-acetate kinetics in myocardium to the pattern of substrate delivery (31) is an additional advantage. However, these advantages are somewhat counterbalanced by the need for more frequent synthesis of the radiopharmaceutical (physical half-life 20.3 min for carbon-11 vs. 109.9 min for fluorine-18) and slightly more intensive computer processing and data analysis.

The extent of improvement in global left ventricular function and clinical outcome after revascularization are related in part to the extent of dysfunctional but still viable myocardium present initially (2,32,33). Positron emission tomography and ^{18}F-fluorodeoxyglucose can identify patients with left ventricular dysfunction due to coronary artery disease in whom successful coronary revascularization will result in an increase in left ventricular ejection fraction and an improvement in functional class (2,33). Moreover, patients who are at high risk for future cardiac events can be identified (33). Thus, the improved identification of left ventricular segments that contain dysfunctional but still viable myocardium by PET with ^{11}C-acetate should facilitate the objective assessment of the need to revascularize myocardium and interventions designed to restore myocardial perfusion, thereby improving patient selection for coronary revascularization.

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